BUILDING A PHARMACEUTICAL PRODUCTION SITE IN GERMANY TODAY

A report by the CDMO
Losan pharma and
case study on integrating
a pellet line

Dr. Johannes Trapp, Losan

We are your one-stop shop solution partner from concept to commercialization.

Analytical Services

We have extensive experience in the development of robust analytical test methods for raw materials, APIs and pharmaceutical products.

Clinical Trial Supply

We support the complete range of clinical trials (preclinical to Phase III) including clinical packaging.

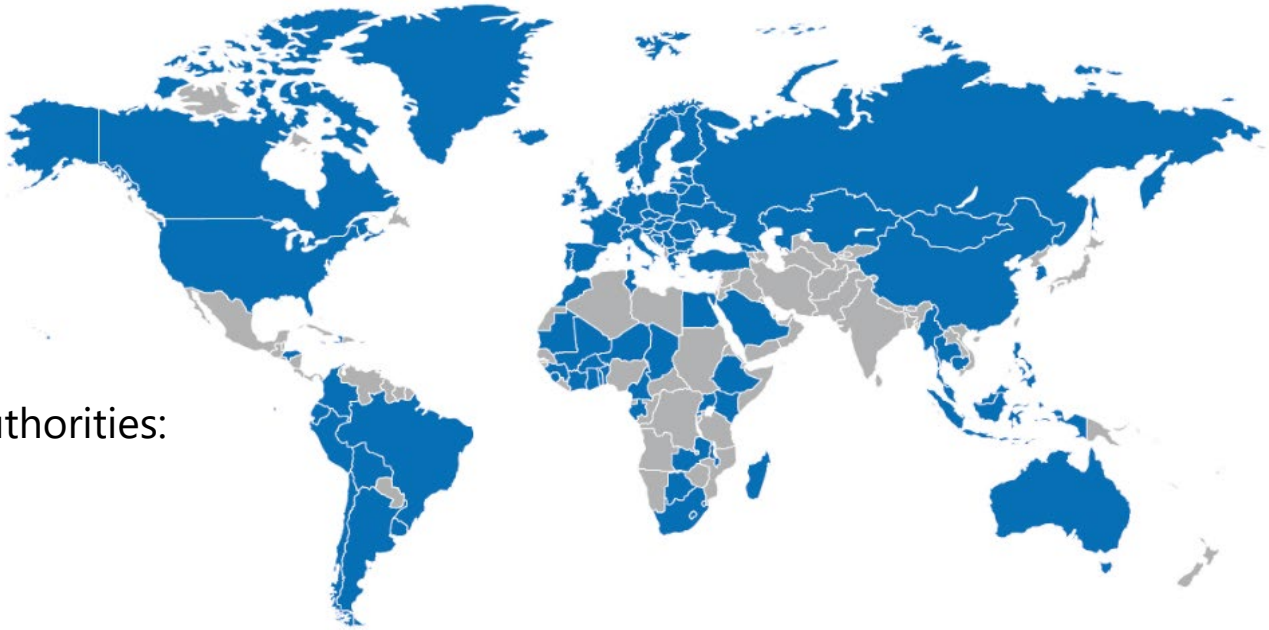
Development Services

We guide you all the way from early-phase development to manufacturing your clinical supply requirements.

Manufacturing and Packaging Services

We provide full service supply (incl. material procurement, tech transfer, process optimisation, validation)

Our accreditations



Losan Pharma GmbH is accredited as drug manufacturer by international authorities:

MHRA, FDA, ANVISA, Saudi-FDA, Turkish MoH, Belarusian Health Authority, Kenyan Health Authority, Uganda MoH, Yemen MoH.

The medicines we produce are distributed by our customers in **over 70 countries.**

30 years of experience

With our 800+ employees, we develop and manufacture modern medicinal products on behalf of our customers in the pharmaceutical industry worldwide.

Founded 1992

Employees 800+

Turnover > 125 mio € / year

Two sites in Germany

Neuenburg am Rhein

Eschbach, Gewerbepark Breisgau

Owner Dr. Falk Pharma GmbH

Company milestones

1992 Losan Pharma is founded

1996 Sustained release and saliva resistant coating technologies

2000 Extrusion and spheronisation technologies

2004 Start of stick pack production

2006 First product on US market

Plant expansion in Neuenburg

2007 Dr. Falk Pharma acquires Losan Pharma

2010 Hot melt extrusion and Nanotechno-logies

2015 New warehouse in Neuenburg

2016 First Losan Scientific Drug Delivery Conference on formulation technologies

2017 New site in Eschbach expanding our packaging and quality control capacities

2019 New R&D analytical laboratory

2020 Starting semi solids and liquids production

2021 New R&D formulation rooms.

2023 New administration building in Eschbach. Start of construction of the new manufacturing site in Eschbach.

2024/25 Further expansion of R&D capacity in Neuenburg. Opening of new manufacturing site in Eschbach.

Our sites

Neuenburg am Rhein

- Manufacturing and packaging of solids, semi solids and liquids
- Contract development & Clinical trial supply
- Starting material sampling, testing and release
- Stability testing
- Storage

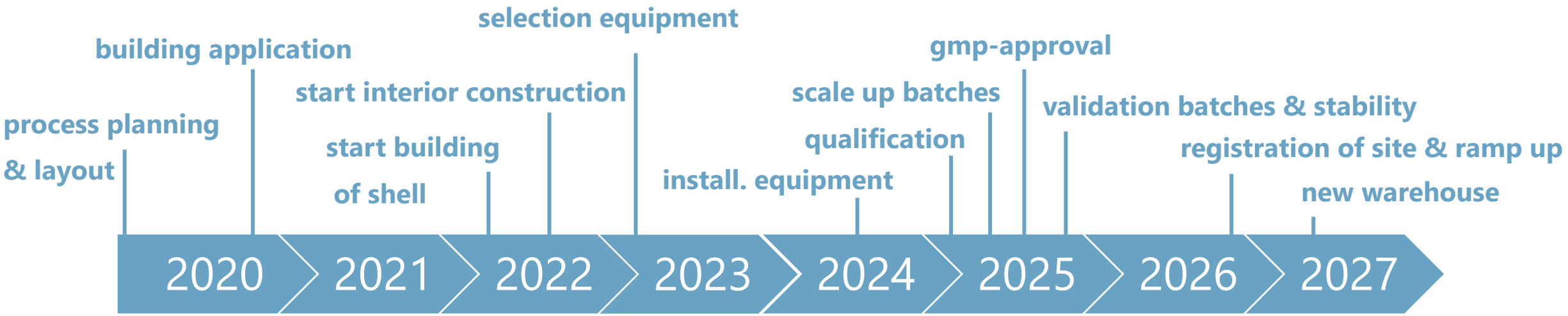
Eschbach

- Primary and secondary packaging
- 11 packaging cabinets for stick packs, blisters and sachets
- QC finished products
- Administration
- Manufacturing (coming soon)

Expansion at our Eschbach site

- Packaging building 2017
- Administration building 2023
- Production building 2025
- Logistics centre 2026

Expansion at our Eschbach site



Layout **manufacturing** site

Pellets Line

Blending

Fluidbed Coating

HSM & Dryer

Compression

Drum Coater

Infrastructure

Connection to warehouse

Connection to packaging

Pellets

- Pellets are small, spherical cores with an average diameter of 0.1 to 3 mm.
- The surface of pellets is typically smooth and not very porous.
- Pellets can be filled into stick packs for direct application or into capsules.
- Furthermore, pellets can be formulated as immediate release or sustained release dosage forms and can also be coated to deliver drugs to specific sites of action in the gastrointestinal tract.

Pelletization is possible using drug layering onto starter pellets or by ring die extrusion and spheronization:

Drug Layering

Layering is similar to a film coating process. One or more active ingredients are applied in layers as a solution or suspension onto starter pellets (e.g., sugar starch, MCC or tartaric acid spheres with a size range of 0.1 to 2 mm).

Extruded Pellets

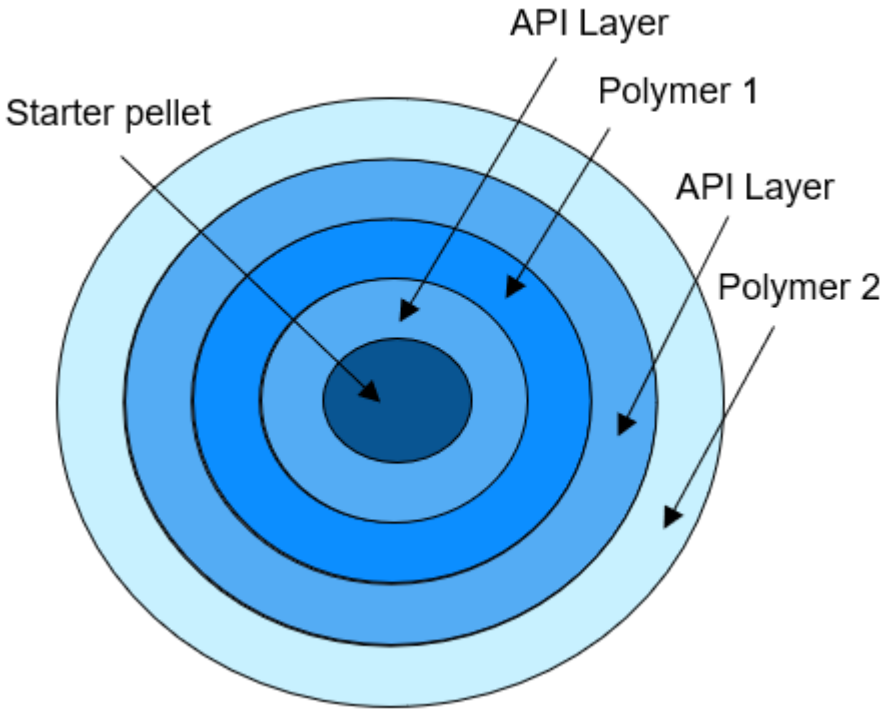
Extrusion pellets are produced by a granulation process in which a powder mixture of API and excipients are agglomerated using a binding liquid. The material is then processed in a ring die extruder to produce high density extrudates. These extrudates are finally shaped into pellets.

Pellets can further be processed to various dosage forms:

- Filled into Capsules
- Filled into Stick Packs
- Compressed to Tablets

Customized release

Example concept – Dual Release Pellets



Modified Release Formulations can help to reduce side effects and/or increase the efficacy of a drug product.

With our extensive know-how in fluid bed coating we have the capability to layer different coatings on each pellet. We can provide pellets with targeted release by using pH dependent coatings or extended release by using pH independent swelling coatings.

Matrix Formulations as a combination of immediate release and extended release pellets filled in a capsule or stick pack can further be a huge benefit for patients (e.g. a medication which needs three tablets per day can be reduced to one stick/capsule once a day, or it can help to secure the night time).

Improve patient compliance

High Drug Load

Pellets filled in stick packs are a great alternative dose form for elderly people or kids having difficulties in swallowing big tablets.

Compared to tablets or capsules pellets in stick packs can achieve a much higher drug load.

With our patented Vismon coating we help the patients to swallow the pellets when direct applicated. The coating significantly improves the swallowing of large amounts of multiparticulate systems without water. Upon contact with saliva, the coating swells moderately and a viscous and firm pulp of multiparticulates is created.

TASTE MASKING

Taste masking is very important for pellets which are filled into stick packs for direct application.

Taste masking is performed by fluid bed coating.

Pleasant tasting flavour mixtures can further improve the mouthfeel and taste for direct applications (ideal for paediatric formulations).

Advantages

Of Pellets

- Flexibility in dosage form design and modification of release profiles
- Possibility to combine incompatible drugs
- Higher drug load possible compared to tablets.
- Easy to swallow thanks our Vismon® coating technology
- Avoid high local concentrations as they disperse freely in the GI tract
- Minimise potential side effects without decreasing bioavailability.
- Compared to monolithic forms, multiparticulate distribution of particles in the GI tract reduces fluctuations in plasma levels.
- Increased mechanical strength of the dosage form

Our services

- Formulation Development
- Analytical Development
- Clinical Trial Supply (through all clinical phases)
- Scale-up from pilot scale to commercial scale
- Commercial Manufacturing
- Extensive Down Stream Capabilities

Pelletization equipment

Granulation / Drying

- **Lab/Pilot scale & Production scale**

Extrusion / Spheronization

- **Lab/Pilot scale & Production scale**

Fluid Bed Coating

- **Lab/Pilot scale & Production scale**

Dose Form Capabilities (Encapsulation, Stick Packs)

- **Encapsulation & Stick Pack Filling**

Pelletization equipment

Existing line

Semi-Continuous Process:

(right to left)

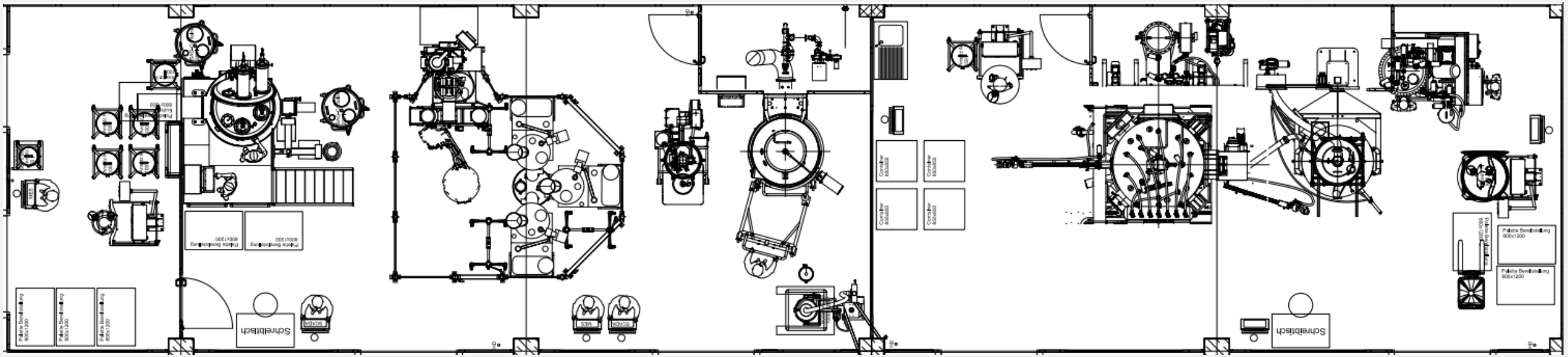
- High shear mixer Diosna
- Ring die extruder Schlüter PP240
- Spheronizer Schlüter 2xRM700
- Screening machines Russel Finex
- Fluid bed dryer HDGC 800
- Vacuumtransfer Volkmann

- Output: up to 1000 kg API pellets/day

Pelletization equipment

New line

Granulation | Extrusion & Rounding | Drying | Fluid Bed Coating



Granulation	Extrusion & Rounding		Drying	Fluid Bed Coating	
preparation of gran liquids	product transfer vacuumfeeder	sieving	yield	preparation of coating liquids	sieving
DIOSNA P1250	**Kahl & Gabler R-700**		**Diosna CAP600**	**Syntegon HDGC1200**	**Ystral**

Layout line

Granulation

High-shear mixer DIOSNA P1250

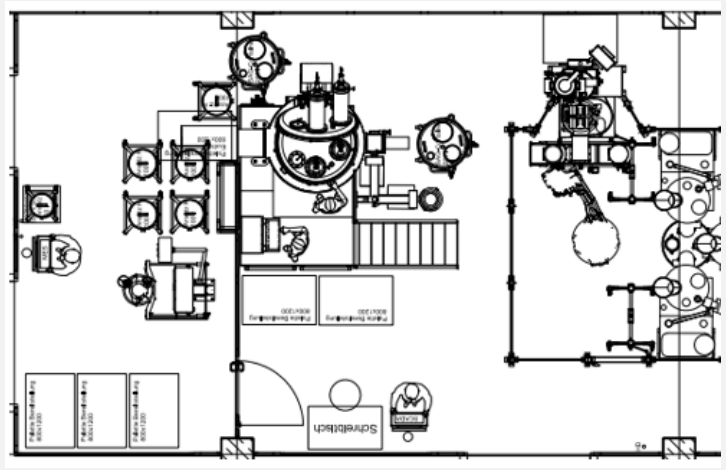
Two filters for fast loading of compounds

2 pumps for low and high viscosity liquids

Inline conical seaving Frewitt CW-150

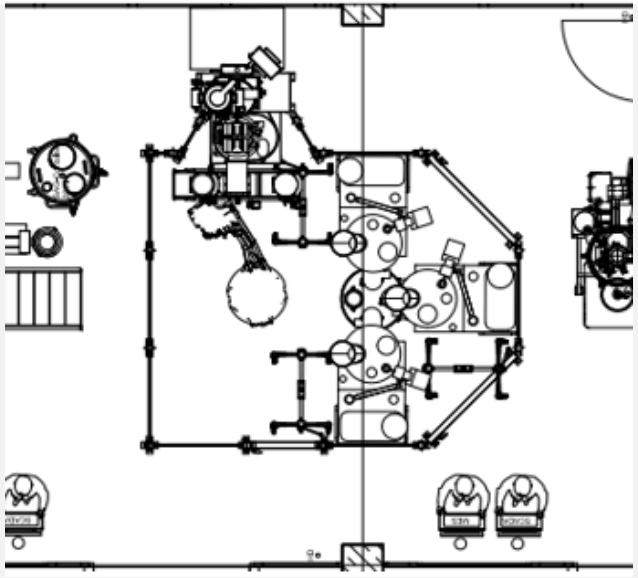
WIP-Cleaning & DIOSNA-Toollift for inspection of seals

Interface to Losan Manufacturing Execution System



Layout line

Spheronization and Extrusion



Extruder Kahl with Feeder

Feeder is controlled by a balance

up to 180 kg / hour

Portions of extrudate are colleted

Automated transfer to the sheronizer with robotics

Interface to Losan Manufacturing Execution System

Spheronizer Gabler R-700-LH

Unit with 3 Spheronizer

Heating and cooling of the vessels

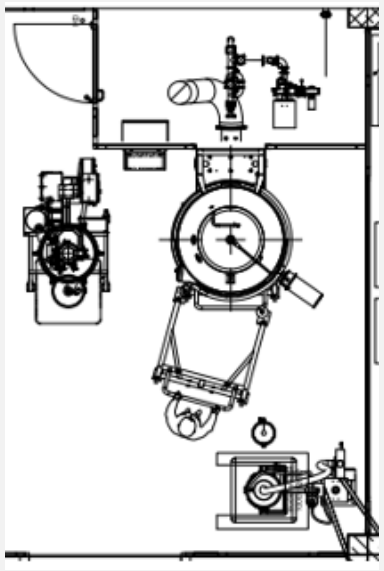
Feeder for Magnesiumstearat

Rounded pellets are transferred to a container

Interface to Losan Manufacturing Execution System

Layout line

Drying



DIOSNA CAP600

Fast charging and discharging (vaccum feeder)

Efficient drying supported by district heating

WIP Cleaning

Interface to Losan Manufacturing Execution System

Vacuumfeeder & Sieving

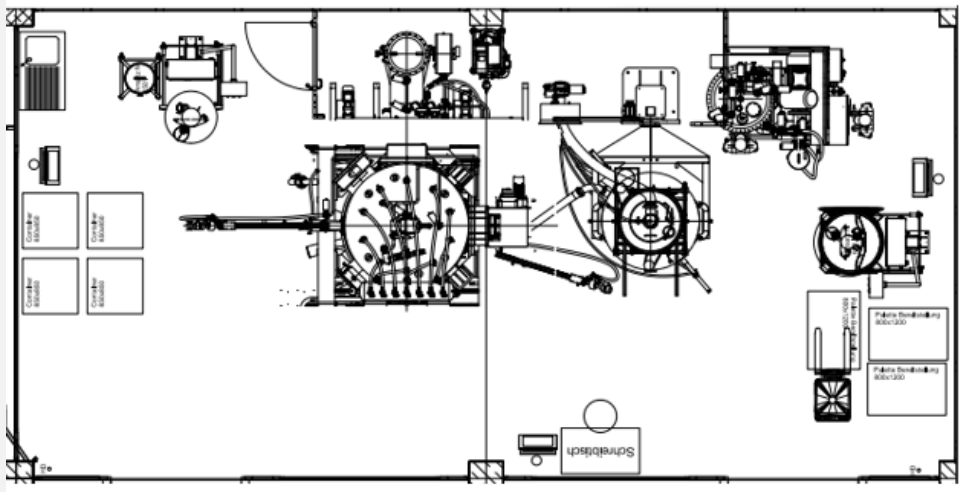
Pellets are collected after rounding

Automated sieving procedure

Collection of pellets in container

Layout line

Fluid Bed Coating



Syntegon HDGC 1.200

High spray rate due to 36 nozzles

Batches up to 1.000 kg

WIP Cleaning

Short process time due to efficient drying

Various stirrer, high shear mixer, inline disperser

How to succeed

Practical Experience / Challengess

- Get the right project team
- Building project vs. machine project
- EHS requirements
- Optimization of manufacturing processes, how far to go?
- Pharmaceutical registration process

Great place to work

“Fair, social and appreciative“

these are the strongest terms with which our employees have distinguished us.

More to discover on our website

www.losan-pharma.com

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THANK YOU FOR YOUR ATTENTION!

Dr. Johannes Trapp, Losan